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Preferences in the management of high-risk prostate cancer among urologists in Europe: results of a web-based survey

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Objective

To explore preferences in the management of patients with newly diagnosed high-risk prostate cancer (PCa) among urologists in Europe through a web-based survey.

Materials and Methods

A web-based survey was conducted between 15 August and 15 September 2013 by members of the Prostate Cancer Working Group of the Young Academic Urologists Working Party of the European Association of Urology (EAU). A specific, 29-item multiple-choice questionnaire covering the whole spectrum of diagnosis, staging and treatment of high-risk PCa was e-mailed to all urologists included in the mailing list of EAU members. Europe was divided into four geographical regions: Central-Eastern Europe (CEE), Northern Europe (NE), Southern Europe (SE) and Western Europe (WE). Descriptive statistics were used. Differences among sample segments were obtained from a z-test compared with the total sample.

Results

Of the 12 850 invited EAU members, 585 urologists practising in Europe completed the survey. High-risk PCa was defined as serum PSA ≥20 ng/mL or clinical stage ≥ T3 or biopsy Gleason score ≥ 8 by 67% of responders, without significant geographical variations. The preferred single-imaging examinations for staging were bone scan (74%, 81% in WE and 70% in SE; $P = 0.02$ for both), magnetic resonance imaging (53%, 72% in WE and 40% in SE; $P = 0.02$ and $P = 0.01$, respectively) and computed tomography (45%, 60% in SE and 23% in WE; $P = 0.01$ for both). Pre-treatment predictive tools were routinely used by 62% of the urologists, without significant geographical variations. The preferred treatment was radical prostatectomy as the initial step of a multiple-treatment approach (60%, 40% in NE and 70% in CEE; $P = 0.02$ and $P < 0.01$, respectively), followed by external beam radiation therapy with androgen deprivation therapy (29%, 45% in NE and 20% in CEE; $P = 0.01$ and $P = 0.02$, respectively), and radical prostatectomy as monotherapy (4%, 7% in WE; $P = 0.04$). When surgery was performed, the open retropubic approach was the most popular (58%, 74% in CEE, 37% in NE; $P < 0.01$ for both). Pelvic lymph node dissection was performed by 96% of urologists, equally split between a standard and extended template. There was no consensus on the definition of disease recurrence after primary treatment, and much heterogeneity in the administration of adjuvant and salvage treatments.

Conclusion

With the limitation of a low response rate, the present study is the first survey evaluating preferences in the management of high-risk PCa among urologists in Europe. Although the

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definition of high-risk PCa was fairly uniform, wide variations in patterns of primary and adjuvant/salvage treatments were observed. These differences might translate into variations in quality of care with a possible impact on ultimate oncological outcome.

Keywords

prostatic neoplasms, prostatectomy, radiation therapy, androgen deprivation therapy, high-risk prostate cancer, survey

Introduction

High-risk prostate cancer (PCa) accounts for up to 40% of newly diagnosed cases, depending on the definition used [1,2]. Despite refinement in patient selection and advances in primary and adjuvant therapies, disease recurrence remains substantial, affecting >50% of patients within 10 years after treatment and carrying a significant risk of progression and death [1,3].

In the absence of high-level evidence, the best management approach for patients with high-risk PCa is still under debate. Guidelines from several scientific societies [4,5] provide useful information, but evidence as to compliance to these is scarce and conflicting [6,7]. All too often, therefore, the ultimate management of high-risk PCa is influenced by the individual preference of the treating urologist, the presence of a multidisciplinary institutional team, local availability of diagnostic and therapeutic technology and other non-medical factors, such as patient socio-economic status, geographical area and medicolegal issues [8–10].

There remains a paucity of data on attitudes of treating urologists in the contemporary PCa literature. In the present study, we explored preferences in the management of patients with newly diagnosed high-risk PCa among urologists practising in Europe through a web-based survey.

Materials and Methods

On 15 August 2013, a specific web-based questionnaire created on surveymonkey.com by members of the Prostate Cancer Working Group of the Young Academic Urologists Working Party of the European Association of Urology (EAU) was sent by e-mail to 12 850 urologists who were included in the mailing list of the EAU members.

Participants were invited to answer a multiple-choice questionnaire including 29 items covering the whole spectrum of diagnosis, staging and treatment of high-risk PCa. Multiple responses were allowed only for a few questions (Appendix S1).

Data collection was stopped 30 days later, on 15 September 2013. All data were processed and analysed using GfK© Romania (GfK Group, Nuremberg, Germany) in accordance with the International Chamber of Commerce/European Society for Opinion and Market Research Code on Market and Social Research [11]. To evaluate whether differences were related to the geographical origin of respondents, Europe was divided into four areas: Central Eastern Europe (CEE), Northern Europe (NE), Southern Europe (SE) and Western Europe (WE [Appendix S2]).

Descriptive statistics were used. Differences among sample segments were obtained from a z-test compared with total sample, performed at a 95% confidence level. A ± 3.9% sampling error was observed. All reported *P* values were two-sided and statistical significance was set at $P = 0.05$. SPSS 21.0 software was used for statistical analysis.

Results

Of the 12 850 invited EAU members, 9829 practised in European countries, and 8234 were urologists. Of these, 585 (7%) completed the survey, 105 (18%) from CEE, 36 (6%) from NE, 281 (48%) from SE and 163 (28%) from WE.

Of the 585 urologists, 246 (42%) were based at an academic hospital (56% in CEE and 28% in WE; $P = 0.01$ and $P < 0.01$, respectively), and 153 (26%) practised in a regional hospital (43% in WE and 11% in CEE; $P = 0.01$ and 0.02, respectively). Of the respondents, 293 (50%) had > 10 years of experience in PCa management, and 223 (38%) were high-volume surgeons, defined as performing >50 radical prostatectomies (RPs) per year. The vast majority of respondents (498/585, 85%) worked within a multidisciplinary team, mostly including oncologists, radiation oncologists and radiologists, this percentage being the highest in WE (98%) and the lowest in CEE (77%; $P = 0.01$ for both).

Definition and Clinical Staging

High-risk PCa was defined as PSA ≥20 ng/mL or clinical stage ≥ T3 or biopsy Gleason score ≥ 8 by the majority of respondents (392/585, 67%), with no significant geographical variations (Fig. 1).

The most commonly performed imaging examinations for clinical staging were bone scan (74%, 81% in WE and 70% in SE; $P = 0.02$ for both), MRI (53%, 72% in WE and 40% in SE; $P = 0.02$ and $P = 0.01$, respectively) and CT (45%, 60% in SE and 23% in WE; $P = 0.01$ for both). Pre-treatment predictive tools were used on a routine basis by 62% of the respondents, without significant geographical variations. Partin tables and

Fig. 1 Preferences for definition of high-risk prostate cancer. Numbers are proportions of respondents per geographical area. Total refers to the entire European sample ($N = 585$). PFS, progression-free survival.

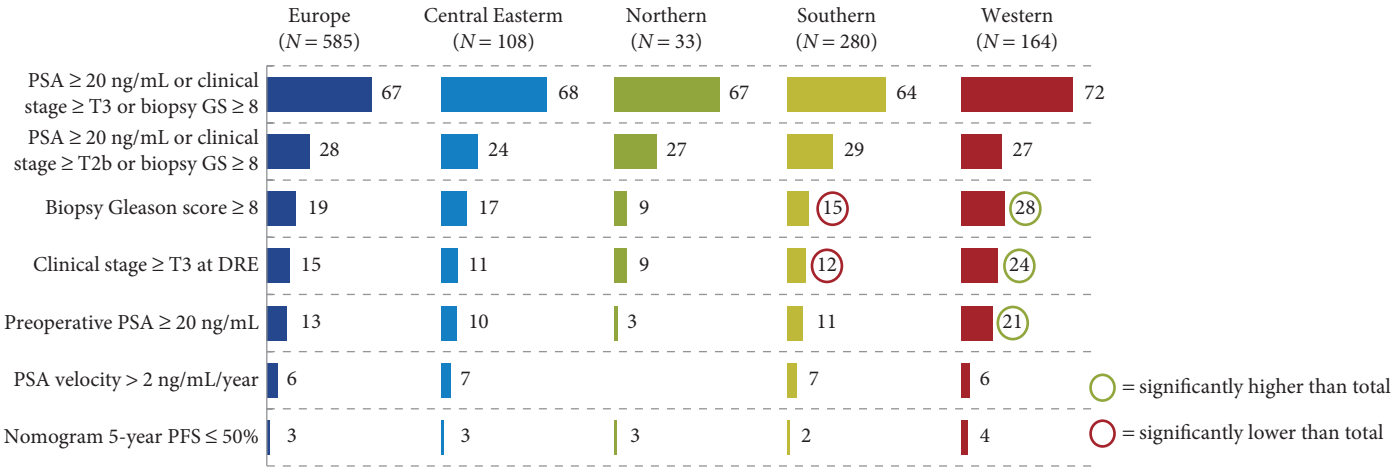
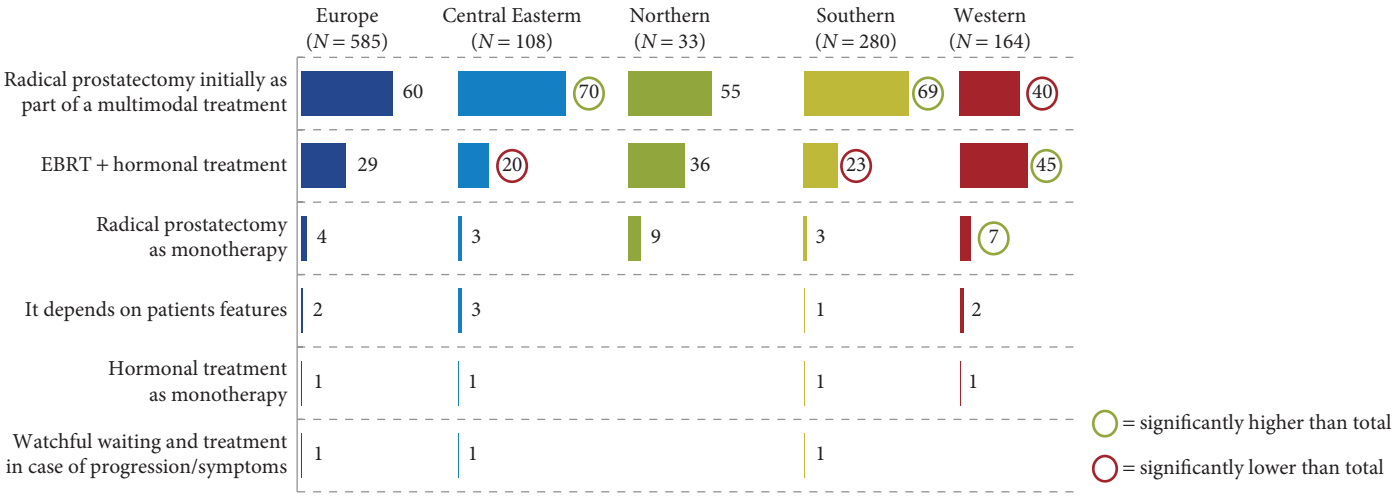


Fig. 2 Preferences for initial management of high-risk prostate cancer. Numbers are proportions of respondents per geographical area. Total refers to the entire European sample ($N = 585$). EBRT, external beam radiation therapy.



D'Amico risk classification were the most frequently used (50 and 41%, respectively, without significant geographical variations).

Initial Treatment

The preferred initial treatment was RP as part of a multiple-treatment approach for 60% of the respondents (70% in CEE and 40% in WE; $P = 0.02$ and $P < 0.01$, respectively), followed by external beam radiation therapy (EBRT) with androgen deprivation therapy (ADT) by 29% (45% in NE and 20% in CEE; $P = 0.01$ and $P = 0.02$, respectively), and RP as monotherapy by 4% (7% in WE; $P = 0.04$ [Fig. 2]).

When treatment was RP, the open retropubic approach was the most frequently adopted (58% overall, 74% in CEE and 37% in WE; $P < 0.01$ for both [Fig. 3]). Attempted nerve-sparing was systematically avoided by 60% of the respondents (73% in SE and 47% in CEE; $P = 0.02$ for both).

Pelvic lymph node dissection (PLND) was routinely performed by 96% of respondents (98% in SE and 88% in NE; $P = 0.03$ and $P = 0.02$, respectively). A standard (i.e. external, internal and obturator nodes bilaterally) and extended (i.e. common iliac, external, internal and obturator nodes bilaterally) dissection template was equally adopted (31 and 30% of respondents, respectively), with no significant geographical variations (Fig. 4). Intra-operative frozen sections during PLND were routinely performed by 13% of the respondents (19% in CEE; $P = 0.03$), and 46% of respondents (63% in WE; $P = 0.02$) abandoned RP if lymph node invasion

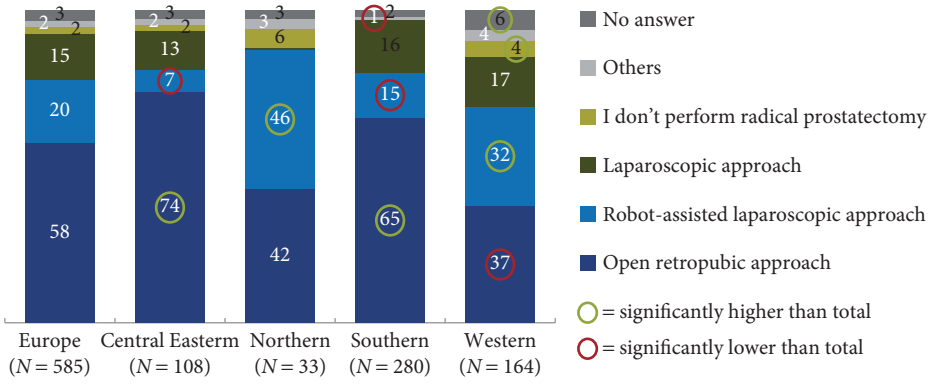
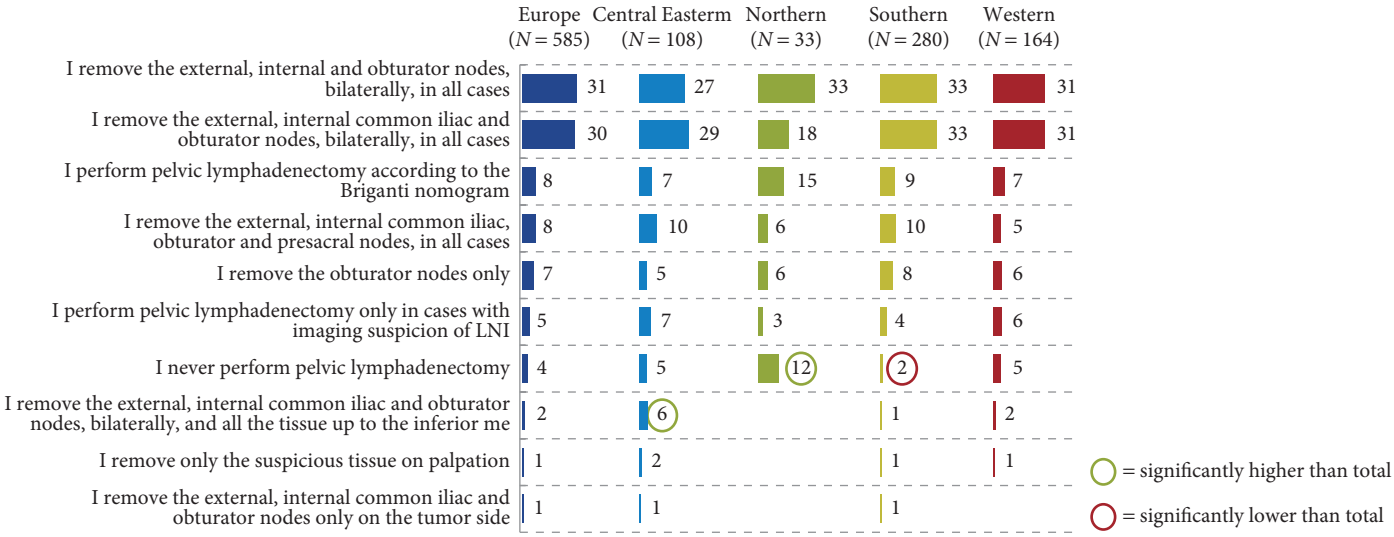


Fig. 3 Preferences for radical prostatectomy approach for high-risk prostate cancer. Numbers are proportions of respondents per geographical area. Total refers to the entire European sample ($N = 585$).

Fig. 4 Preferences for pelvic lymph node dissection template at the time of radical prostatectomy for high-risk prostate cancer. Numbers are proportions of respondents per geographical area. Total refers to the entire European sample ($N = 585$). LNI, lymph node invasion.



was proven. Regarding the minimal nodal yield required for an accurate PLND, opinions varied, with some respondents (56%) considering that the minimum number should exceed 10, and others (37%) judging that dissection of an anatomically defined pelvic region was more important than lymph node count.

Definition and Treatment of Disease Recurrence

Biochemical recurrence (BCR) after RP was defined as any rise in PSA level ≥0.2 ng/mL, confirmed with a second measurement at least 1 month apart, by 47% of the respondents, while 26% defined BCR as three consecutive rises of PSA ≥0.2 ng/mL (Fig. 5). No significant geographical variations were observed.

Regarding the definition of local recurrence after RP, responses varied from a positive biopsy from anastomosis site/pelvis (32%) to abnormal findings on MRI (29%) and to positive surgical margins (24%), with no significant geographical variations (Fig. 6).

In all, 47% of the respondents defined BCR after EBRT as any rise in PSA level ≥2 ng/mL above the post-treatment nadir, while 37% of respondents defined it as three consecutive PSA rises above the post-treatment nadir. No significant geographical variations were observed.

Concerning adjuvant/salvage treatment after RP, 53% of respondents (63% in SE and 36% in NE; $P = 0.02$ and $P = 0.01$, respectively) offered adjuvant EBRT only if surgical margins were positive, most often within 3 months after surgery, while 43% (51% in WE; $P = 0.02$) recommended salvage EBRT in the case of BCR (Fig. 7). Adjuvant ADT was offered only if lymph nodes were positive by 62% of respondents (73% in SE, 45% in WE; $P = 0.01$ for both), while salvage ADT was offered

Fig. 5 Preferences for definition of biochemical recurrence after radical prostatectomy for high-risk prostate cancer. Numbers are proportions of respondents per geographical area. Total refers to the entire European sample (*N* = 585).

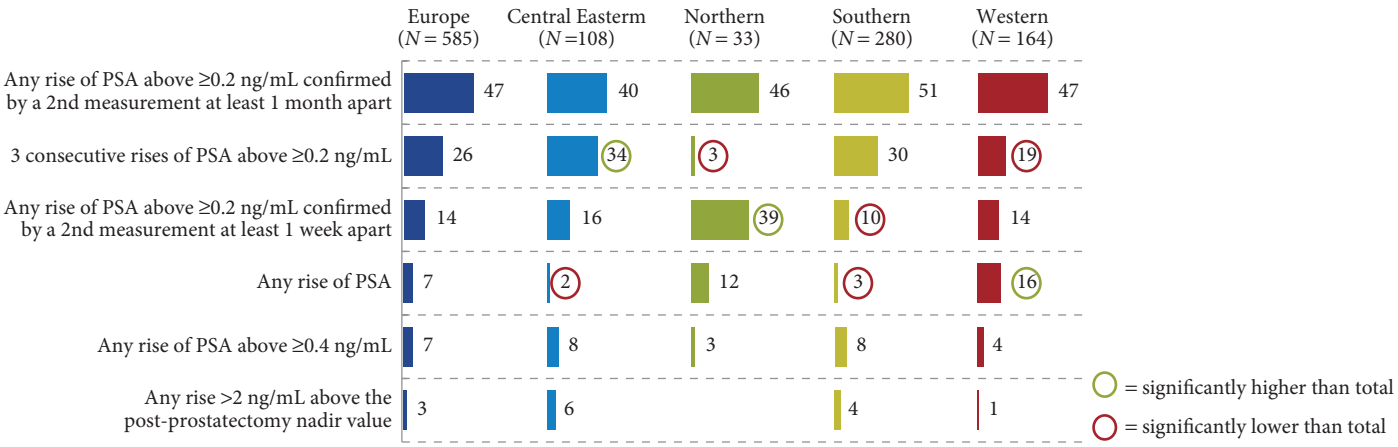
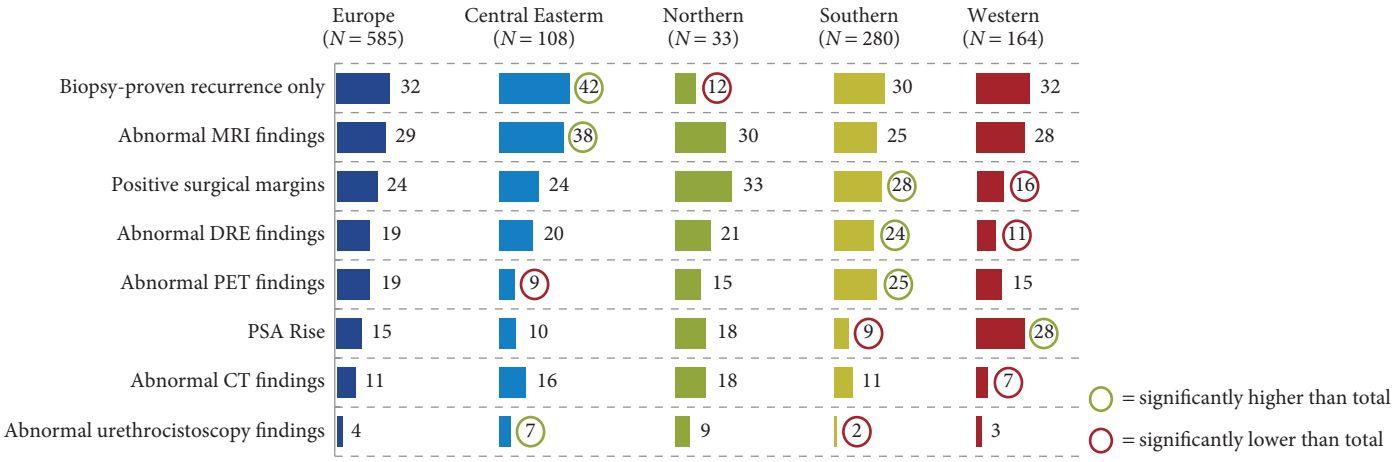


Fig. 6 Preferences for definition of local recurrence after radical prostatectomy for high-risk prostate cancer. Numbers are proportions of respondents per geographical area. Total refers to the entire European sample (*N* = 585). PET, positron emission tomography.



in the case of BCR and distant metastases by 39% (53% in CEE, 26% in WE; $P = 0.02$ for both) and 76% (without significant geographical variations) of respondents, respectively (Fig. 8).

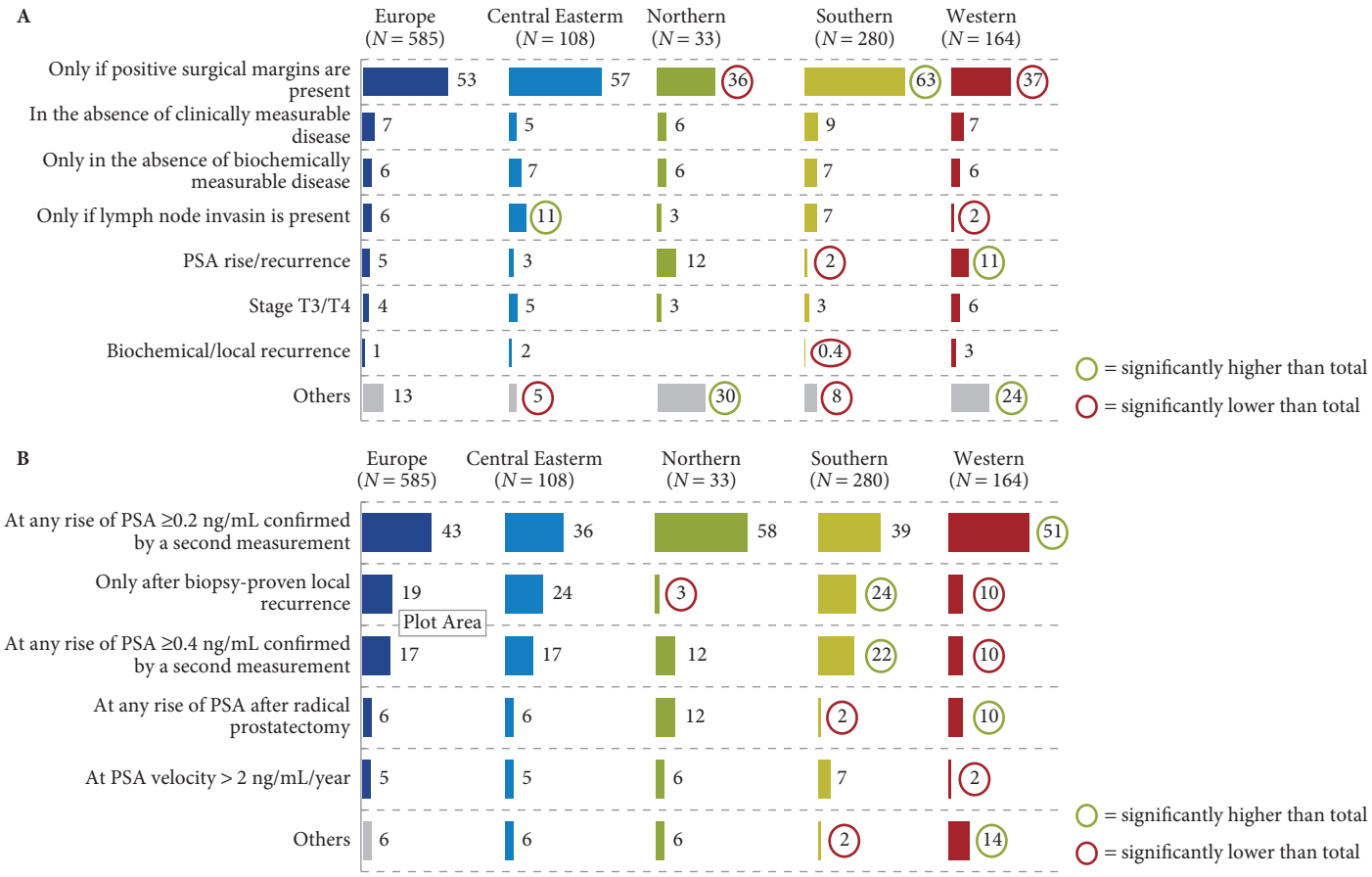
Discussion

The present study is the first international survey evaluating preferences in the management of high-risk PCa among urologists in Europe. There was good agreement on the definition of high-risk disease. The preferred treatment was found to be open RP with either standard or extended PLND as the initial step of a multiple-treatment approach. Consensus on the definition of disease recurrence after primary treatment was weaker, and there was much heterogeneity in administration of adjuvant and salvage therapies. Geographical differences were observed with regard to several questionnaire items.

Several results of our survey may be of interest. First, the definition of high-risk PCa was shared by ~66% of the respondents. The most commonly used definition was any cancer with PSA ≥20 ng/mL or clinical stage ≥ T3 or biopsy Gleason score ≥ 8, which represents the definition published in both the EAU and National Comprehensive Cancer Network (NCCN) guidelines [4,5].This should facilitate the conduct of multinational collaborations for trials on high-risk PCa.

Second, the majority of respondents would offer RP as the initial step of a multiple-treatment approach for PCa. While EBRT with long-term ADT has long been considered the standard of care compared with other treatment methods, over the past decade there has been a surge in the use of RP as primary treatment in selected patients, followed by EBRT in case of adverse pathological features [12]. Both the EAU and NCCN guidelines [5] recommend radiation therapy with ADT

Fig. 7 Preferences for administration of **A**, adjuvant and **B**, salvage external beam radiation therapy after radical prostatectomy for high-risk prostate cancer. Numbers are proportions of respondents per geographical area. Total refers to the entire European sample ($N = 585$).

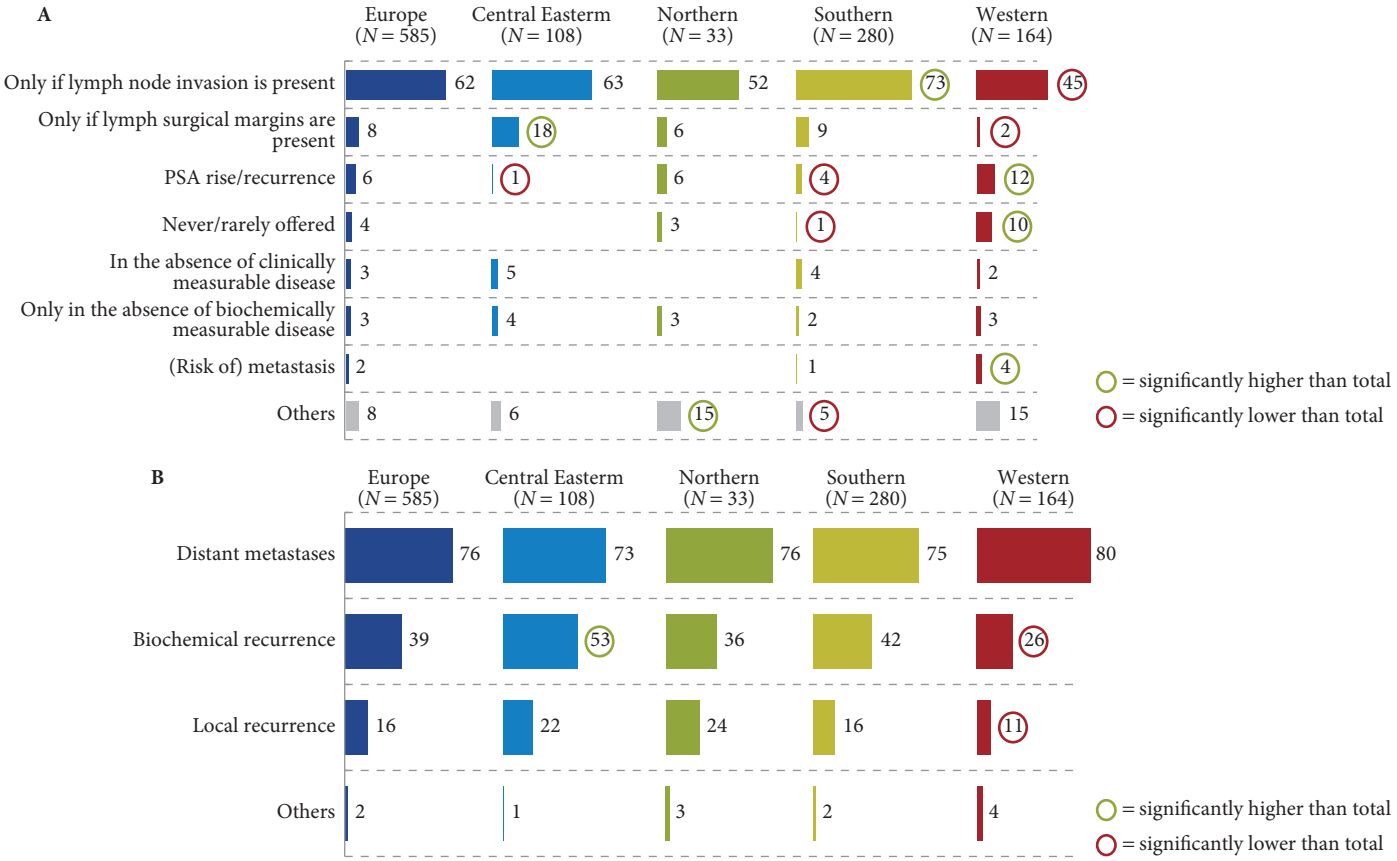


as the preferred treatment for high-risk PCa, and indicate surgery as an option to selected patients with low-volume disease [4] or no fixation to adjacent organs [5]. The findings in the present survey may reflect data from recent population-based studies comparing surgery and EBRT for clinically localized PCa, which have consistently demonstrated a possible benefit of surgery, especially in younger and fitter patients with more aggressive disease [13–16]; however, the target population of our survey were urologists only, which may have biased the choice of treatment towards surgery.

Third, the preferred approach for RP is open (58%), followed by robot-assisted (20%) and laparoscopic (15%). One reason might be the reluctance of urologists to use newer, i.e. robotic, technology in patients with an aggressive form of disease, a finding common to other settings [17]. In particular, the lack of tactile feedback with the robotic approach might have led some surgeons to prefer the open operation for high-risk cases. Despite the growing body of literature reporting on favourable outcomes of robot-assisted RP in high-risk PCa [18], including the evidence that the use of intra-operative visual cues can compensate for lack of tactile feedback [19], the absence of well-designed randomised or head-to-head comparative studies may have generated some uncertainties among health providers. Alternatively, the limited uptake of robot-assisted surgery in several countries in Europe, especially in CEE (where open RP has the highest preference in our survey), may be attributable to health economic reasons. These countries have a lower budget assigned for healthcare and, thus, their interest in investing in costly technology may be limited. Our survey did not evaluate whether a robot was available at the respondent's institution, and, if available, whether a robot-assisted approach would have been favoured over the open one for high-risk PCa; however, in one US study, it has been shown that hospitals with availability of robotic surgery increased the RP volume by ~30 cases/year, while hospitals without robotic facilities decreased the volume by ~5 cases/year [20]. It might thus be anticipated that with increasing dissemination of robotic systems across Europe, these figures will change in favour of the robotic approach.

Fourth, PLND at the time of RP was performed by virtually all urologists; however, despite the currently accepted recommendation to systematically perform an extended PLND in patients with high-risk PCa [4,5], the use of an extended

Fig. 8 Preferences for administration of **A**, adjuvant and **B**, salvage androgen deprivation treatment after radical prostatectomy for high-risk prostate cancer. Numbers are proportions of respondents per geographical area. Total refers to the entire European sample (*N* = 585).



and standard template was equally split among surgeons. Possible reasons not to perform an extended PLND may be the absence of convincing high-level evidence as to its curative role [21], and the potential for greater morbidity [22]. Also, more than one third of respondents considered that the number of nodes removed was not relevant. This is consistent with the findings of recent publications [23,24], rather emphasising the value of an accurate dissection of anatomically determined pelvic regions. Additionally, roughly half of respondents of the minority who routinely perform frozen sections during PLND reported they abandon surgery in the case of lymph node metastases. This practice is reminiscent of the old belief that patients with PCa with positive lymph nodes have a systemic disease with poor prognosis, but increasing contemporary evidence suggests that RP with extended PLND is an important component in multimodal therapy of locally advanced PCa with the potential to improve survival [25].

Fifth, there was much heterogeneity in the definition of disease recurrence after primary treatment and in the use of adjuvant and salvage therapies. The lack of consensus on biochemical and local recurrence has direct implications in the subsequent choice of adjuvant and salvage treatment, as disease progression rates may vary by up to 35% depending on the definition used [1]. Only 53% of respondents would offer adjuvant EBRT in the presence of positive surgical margins, while 43% would consider salvage EBRT after any rise in PSA level ≥0.2 ng/mL confirmed by a second measurement. Accumulating evidence from randomised trials indicates that adjuvant EBRT to the prostate bed after RP favourably influences the course of disease compared with observation in men with adverse pathological features [26]. No similar high-level evidence for salvage EBRT is available, however, although in some observational studies a substantial proportion of patients with high-risk PCa showed a durable response to salvage EBRT, provided that it was administered at the earliest evidence of BCR [27]. Potential concerns discouraging surgeons from adopting an immediate EBRT policy are the detrimental effect on the functional status (i.e. recovery of urinary continence and potency) [26,27], and the risk of overtreatment for many patients who would have never recurred or progressed in the absence of EBRT [26].

Sixth, considerable geographical differences do exist with regard to various aspects of high-risk PCa management. A

similar scenario has been described among urologists of North America [28], as well as for the management of other malignancies, such as breast cancer [29]. Possible reasons are disparities in national health systems, the availability of diagnostic and therapeutic technologies and cultural background.

The present study has some limitations. First, it is subject to volunteer bias, as the majority of invited participants did not respond. Also, there was no pre-determined sample size that was equally representative of each of the four geographical areas in Europe. Respondents from SE accounted for roughly half of the European sample, with the potential to unbalance the results. Furthermore, differences in management patterns within the geographical area were not assessed. It might well be that significant differences in management exist even within the same country. Second, we only focused on urologists and did not include radiation and medical oncologists, which could have led to specialty bias. In a recent national US survey on physician attitudes towards localized PCa [30], in fact, it was shown that urologists and radiation oncologists had different treatment preferences and perception of oncological and functional outcome, with implications potentially relevant to treatment recommendations and patient counselling. Third, the majority of the respondents were urologists practising in academic and tertiary referral centres, which may have different resources and technologies available compared with those practising at regional/county hospitals. Fourth, reasons for individual choice of one treatment over another (e.g. patient age, comorbidity and preferences, or surgeon/hospital experience) were not investigated for either the primary tumour or its recurrence.

In conclusion, with the limitation of a low response rate, the present study is the first international survey to evaluate patterns of management of high-risk PCa among urologists in Europe. Although definition of high-risk PCa was uniform and consistent with common guidelines, the use of RP as the initial step of a multiple-treatment approach, the adoption of a standard PLND template as frequently as an extended one, and a deferred EBRT policy for disease recurrence represent deviations in practice from the guideline recommendations, and warrant further exploration. Moreover, considerable geographical variations in patterns of staging and treatment were observed. This phenomenon may be attributable to the absence of high-level evidence, coupled with variability in local medical infrastructure availability. Whether these differences in standard of care might affect oncological outcomes requires further study.

Conflict of Interest

None declared.

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Abbreviations: PCa, prostate cancer; EAU, European Association of Urology; CEE, Central-Eastern Europe; NE, Northern Europe; SE, Southern Europe; WE, Western Europe; RP, radical prostatectomy; EBRT, external beam radiation therapy; ADT, androgen deprivation therapy; PLND, pelvic lymph node dissection; BCR, biochemical recurrence; NCCN, National Comprehensive Cancer Network.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 European survey exploring patterns of management of patients with newly diagnosed high-risk prostate cancer.
Appendix S2 Countries composing the four geographical areas in which Europe was divided for the purpose of our survey.

